REMARKS

Summary of the Office Action

Claims 6, 9-26, 33, and 40 are pending in the application, of which claims 6, 9-15 and 39 are under examination. Claims 16-26 and 33 are withdrawn from consideration as being drawn to a non-elected invention. Support for newly added claim 40 can be found, for example, on page 11, lines 15-16.

Claims 6 and 9-15 are rejected as lacking enablement under 35 U.S.C. § 112, first paragraph, and claims 6, 10, 11, and 13-15 are rejected as lacking sufficient written description under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 6 and 9-15 are rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. According to the Examiner, the rejection is based upon the reasons of record.

The present rejection is based on two main areas of concern: (1) whether Applicants have enabled the claimed method to overcome certain hurdles to achieve "effective" therapies and (2) whether Applicants have enabled the use of any importation competent signal peptide to import any protein or peptide. Regarding the first concern, Applicants continue to assert that they are not required to enable the method to achieve the effects and avoid the pitfalls presented in the rejection. The Examiner stated in the Advisory Action mailed January 18, 2006, that, "Applicant should explicitly state what those [practical applications other than therapy] are and where they are contemplated in the specification." However, that is not a requirement under 35 U.S.C. 112, first paragraph. A valid rejection must be based on what is claimed. Regarding the second concern, Applicants note the concerns expressed in the rejection are merely speculative as they relate to the claimed method and Applicants provide further evidence that both charged peptides and larger proteins can be imported to cells both *in vitro* and *in vivo*.

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The Examiner states that in seeking to determine whether the disclosure adequately teaches the skilled artisan how to make and use what is claimed, the Examiner consulted the specification to determine how the inventor envisioned the practical application of the claimed

method. The Examiner then goes on to state that the teachings of the specification, with regard to using the claimed method, are directed to therapeutic application and would require undue experimentation to further develop the method such that it could be used to provide a therapeutic outcome.

In consulting the specification to determine how the inventor envisioned the *practical application* of the claimed method, the Examiner went beyond what is required under the enablement statute. All that is required of the Examiner is to consult the specification for how the *claimed method* is to be used. Anything beyond that analysis falls in the realm of an analysis of utility, and that analysis should be severed from the test of enablement. Section 2164.01(b) of the MPEP states, "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)."

The claims are drawn to a method of importing an intracellular peptide, polypeptide, or protein into a cell in a subject. The claims are fully supported by the specification. The rejection is improper in its focus on effects not recited in the claims and as a result much of the argument and reasoning in the rejection is not relevant to enablement of the present claims. Only that which is claimed need be enabled.[1] Applicants direct attention to *In re Gardner*, 475 F.2d 1389, 1392 (CCPA 1973), *reh'g denied*, 480 F.2d 879 (CCPA 1973), where the court emphasized that the subject matter within a broad claim need not be shown to have the same degree of utility; it is sufficient if the specification adequately discloses some use for all of the subject matter.[2] The law does not require that every imaginable result of a method claim that is not excluded by the claim be enabled.

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[1]see *Christianson v. Colt Industries Operating Corp.*, 822 F.2d 1544, 1565, 1 USPQ2d 1241, 1255 (Fed. Cir. 1987), *vacated, and remanded with instructions to transfer appeal to Court of Appeals for the Seventh Circuit*, 108 S. Ct. 2166, 7 USPQ2d 1109 (1988), *on remand*, 870 F.2d 1292, 1299, 10 USPQ2d 1352, 1357 (7th Cir. 1989) ("Because only the claimed invention receives patent law protection, the disclosures need generally be no greater than the claim.")("The 'invention' referred to in the enablement requirement of section 112 is the *claimed* invention").

[2]See also *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762 (Fed. Cir. 1984) ("the fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility."); *Ex parte Hozumi*, 3 USPQ2d 1059, 1060-61 (Bd. Pat. App. & Int'f 1987) (as to examiner's Section 112 rejection "based on an asserted lack of enablement with respect to the utilization of the entire genus disclosed in the antitumor utility disclosed": "it is not necessary that all of the compounds claimed be useful for every utility disclosed in an application"); *Ex parte Cole*, 223 USPQ 94, 95 (PTO Bd. App. 1983) ("We know of no statutory or case law requiring each and every compound within a claim to be equally useful for each and every contemplated application.").

The proper analytical framework for analyzing embodiments within the scope of a claim is to assess each embodiment for enablement in terms of what is claimed. As discussed above, the standard for enablement for the use of any given embodiment is low (see footnote 2). Thus, every embodiment encompassed by the present claims need only be capable of administration and need only result in importation. That is all that is claimed and that is all that need be enabled. As long as each embodiment of the claimed method is capable of this and the claimed result can be obtained without the need for undue experimentation, that embodiment (and, collectively, the entire claim), is enabled. The fact that some embodiments will accomplish much more (therapeutic effects, for example) does not mean that Applicants are required to enable such effects. It is legal error to pick a possible, but unclaimed, effect of the method and then require that that effect be enabled.

All that Applicants claim is a method involving administering to a subject a complex comprising the peptide, polypeptide, or protein linked to a mammalian hydrophobic importation competent signal peptide. The only effect required by the claim of this administration is importation the peptide, polypeptide, or protein. The claims simply do not require avoiding systemic delivery of toxins. A toxin could be delivered to cells using Applicants' method and it is not the place of the Patent Office to require that such an embodiment be excluded from the claims. The rejection has failed to cite authority for requiring enablement of a feature (targeted delivery of toxins) not recited in the claims. In contrast, Applicants have cited legal authority to the contrary.

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The Examiner contends that the claims are not enabled for importation of any peptide, polypeptide, or protein into any cell because the ability of an importation competent signal peptide to deliver any given peptide, polypeptide, or protein into a cell would have to be determined on a case-by-case basis. The Examiner then quotes the Background section of the specification, which sets up the previous drawbacks of peptide delivery into cells, and uses that to make the point that the movement of any peptide across a membrane is unpredictable. However, the MPEP (section 608.01(c)) states the function of the Background section is as follows: "Where applicable, the problems involved in the prior art or other information disclosed which are solved by the applicant's invention should be indicated." Applicants would like to

point out that the statements made in the Background section simply stated the previous problems of the prior art, as required by the MPEP. Furthermore, the Examiner does not quote the end of the Background section, which states that, "The present invention solves this long-felt, broad spectrum problem by providing a method of importing a biologically active molecule into a cell using mechanisms naturally occurring in cells and thus avoiding damaging the target cells. Additionally, the present method can be used to import molecules into large numbers of cells, including organs. Thus, this versatile inventive method can be employed in numerous treatments of diseases and disorders." (Page 3, lines 12-17 of the specification.)

The claimed method is based on the discovery that hydrophobic signal sequences can be used to internalize peptides, proteins and other molecules. While it was and is understood that proteins and other molecules can cross plasma membranes via pores, phagocytosis, endocytosis, invagination of the plasma membrane and through cell surface receptor-mediated translocation, as are discussed in the Background section of the patent application, these are not the mechanisms by which the present method operates or which the present method requires (see, for example, Figure 5 in Veach et al., (2004) *J. Biol. Chem.* 279:11425-31). Thus, any problems or difficulties with the use of other mechanisms of importation are not relevant to enablement of the claimed method.

Contrary to the theory of the rejection, Applicants have provided evidence that a variety of proteins can be imported using the claimed method. Jo et al., Nature Medicine Vol. 11(8):892-898) (of record), show that a recombinant cell-penetrating form of SOCS3 (CP-SOCS3; 225 amino acids long) was delivered by intraperitoneal injection, was taken up intracellularly, and was able to counteract SEB-, LPS-, and ConA-induced inflammation *in vivo*. A membrane-translocating motif (MTM) composed of 12 amino acids from a hydrophobic signal sequence from fibroblast growth factor 4 was attached to the N-terminal or C-terminal ends to mediate uptake into cells. Thus, the importation of the 225 amino acid SOCS3 protein described in Jo et al. demonstrates that large and charged proteins can be imported using the claimed method. This evidence follows a prior demonstration of successful importation of Cre recombinase into cells and animal by Jo et al, Nature Biotechnology 19:929-933 (2001) (Exhibit LL).

Liu et al., J. Biol. Chem. 279:19239-19246 (2004) ("Liu A"; of record), describes the *in vivo* delivery, importation and effect of an inhibitor of nuclear transport. Liu A used an importation competent signal peptide as claimed (see page 19240, left column, top) and established that the signal peptide was required for cell importation (see page 19241, paragraph bridging columns). Liu et al., J. Biol. Chem. 279:48434-48442 (2004) ("Liu B"; of record), describes the *in vivo* delivery, importation and effect of an inhibitor of nuclear transport (see Abstract). Liu B used an importation competent signal peptide as claimed, and no cell-specific targeting feature was used (see page 48435, left column, first paragraph and first paragraph of Experimental Procedures; page 48436, right column, top). Liu et al., Proc. Natl. Acad. Sci. USA 93:11819-11824 (1996) ("Liu C"; of record), described successful importation using a different signal sequence (see page 11819, left column, bottom).

With this response, Applicants submit Exhibit A as further evidence. Exhibit A describes the product Chariot™, manufactured by Active Motif, Inc., which is a hydrophobic, importation-competent signal peptide (see U.S. Patent 6,841,535 for a description of the Chariot™ signal peptide, attached with the relevant portion highlighted as Exhibit B). This signal peptide has been used with 29 different proteins of widely varying sizes, conformations, and structures (Exhibits C-JJ). This is direct evidence that a widely divergent group of proteins can, and have, been imported into a cell using a hydrophobic importation competent signal peptide, as claimed.

The Examiner has also argued that undue experimentation would be required to practice the method using the broad scope encompassed by the importation competent signal peptide of the claims. Applicants previously argued that signal peptides can be selected from the SIGPEP database, which also lists the origin of the signal peptide. The Examiner states that determining which embodiments that were conceived, but not yet made, would be inoperative or operative would clearly require expenditure of more than is normally required in the art.

Applicants again note that enablement requires enablement of only a single use of the invention. For the present method, all that those of skill in the art need do is choose a signal peptide as described in the specification and a peptide, polypeptide or protein to be imported. Applicants assert that any selected signal peptide can be tested for its ability to function as an importation competent signal peptide, using routine screening methods that employ the *in vitro*, *ex vivo*, and *in vivo* teachings set forth throughout the entire specification, including the

Examples, together with what was already known in the art. Accordingly, identification of additional importation competent signal peptides is routine experimentation, not undue experimentation, and the present methods, as claimed herein, are fully enabled in this regard.

As further evidence, Applicants submit Exhibit KK. As stated before, the SIGPEP database discloses multiple examples of signal peptides that can be used with the claimed methods. Exhibit KK is a list of over 500 signal peptides that have been experimentally verified to act as signal peptides in mammals. Each of them fits the description of signal peptides given in the claims: hydrophobic and importation-competent. Each is within the size range of 10-50 amino acids long, and each is comprised of at least 50% hydrophobic residues. Therefore, over 500 examples exist of signal peptides that are useful with the claimed method. Furthermore, as previously stated, any selected signal peptide can be tested for its ability to function as an importation competent signal peptide, using routine screening methods that employ the *in vitro*, *ex vivo*, and *in vivo* teachings set forth throughout the entire specification, including the Examples, together with what was already known in the art.

Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

Claims 6, 10, 11, and 13-15 are rejected under 35 U.S.C. § 112, first paragraph, as lacking sufficient written description. The Office Action asserts that Applicants did not have possession of the entire genus of importation competent signal peptides, but only a method for how to identify an importation competent signal peptide experimentally. Applicants respectfully traverse.

The Examiner has stated that there is an "absence of any clear nexus of structure and function even ten years after the effective filing date of the instant application." (Page 14 of the Office Action.) It appears that the Examiner does not recognize the teaching of "hydrophobic region" as a structural limitation, but is requiring the applicant to provide specific amino acid sequences of the signal sequences, which is not required under the Written Description Guidelines, and which would unjustifiably limit the scope of the claims.

Written description does not require complete structural information. Rather, written description only requires that sufficient written description be provided such that the subject matter of the invention can be distinguished by those of skill in the art. Applicants have

provided a clear written description of both the subject matter of the claims and of what is required to fulfill the scope of the claims. In particular, Applicants have provided in the specification sufficient written description of the importation competent signal peptides that are to be used in the claimed method. The specification defines importation competent signal peptides as "a sequence of amino acids generally of a length of about 10 to about 50 or more amino acid residues, many (typically about 55-60%) residues of which are hydrophobic such that they have a hydrophobic, lipid-soluble portion" (page 10, lines 25-28). The specification notes that the hydrophobic portion of a signal peptide "is a common, major motif of the signal peptide, and it is often a central part of the signal peptide of protein secreted from cells. A signal peptide is a peptide capable of penetrating through the cell membrane to allow the export of cellular proteins" (page 10, lines 28-31). The specification also gives the Example of SN50 (page 29) as well as many other signal peptides, such as those found in the SIGPEP database. As discussed above, over 500 sequences in the SIGPEP database (http://proline.bic.nus.edu.sg/ sigpep/) fit the description of the signal peptides disclosed in claims. Therefore, the written description requirement is met, in that the Applicant has clearly shown possession of the importation competent signal peptides. This is certainly sufficient to describe the importation competent signal peptides to be used in the claimed method.

The Examiner argues that, "one of skill in the art would not have been able to correlate the function of an IMPORTATION COMPETENT signal peptide with the structure at the time the application was filed." (Advisory Action). However, it is Applicant's contention that any of the signal peptides found in the SIGPEP database, and others fitting the description of the signal peptides described in the application, can be importation competent, and one of ordinary skill in the art could have easily ascertained these molecules.

Furthermore, the signal peptides of the instant claims are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend, and therefore the Examiner's arguments are inapposite to both *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997) and *Enzo. Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003). In *Amgen*, the claims of Amgen's patents referred to types of cells that can be used to produce recombinant human EPO. TKT (Amgen's opponent) argued that, because the Amgen patents did not describe the structure of the claimed cells, the patents failed

to provide adequate written description of the claimed subject matter as required by *Eli Lilly* and *Enzo*. The court in *Amgen* rejected this argument, holding that Amgen's claims, including the recited cells, were adequately described in Amgen's patents. The court noted that unlike in *Eli Lilly* or *Enzo* "the claim terms at issue here [in *Amgen*] are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend....This difference alone sufficiently distinguishes Eli Lilly, because when used, as here, merely to identify types of cells (instead of undescribed, previously unknown DNA sequences), the words 'vertebrate' and 'mammalian' readily 'convey distinguishing information concerning [their] identity' such that one of ordinary skill in the art could 'visualize or recognize the identify of the members of the genus.'" Like the cells of *Amgen*, the claimed importation competent signal peptides are well known biological materials; well classified and easily recognized by those of skill in the art. As a result, and as in *Amgen*, the present application satisfies the written description requirement for the present claims. Given the well-known nature of signal peptides, and the description and definition of importation competent signal peptides (including their relationship to signal peptides; see paragraph bridging pages 10 and 11), Applicants submit that sufficient written description of the subject matter of the claims is provided.

In view of the above, the specification provides sufficient description of pending claims 6, 10, 11, and 13-15, and this basis of the written description rejection can be withdrawn.

CONCLUSION

In view of the above amendments and remarks, reconsideration and allowance of the pending claims is believed to be warranted, and such action is respectfully requested. The Examiner is encouraged to directly contact the undersigned if this might facilitate the prosecution of this application to issuance.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $1,475.00, representing $395.00 for the fee for a small entity under 37 C.F.R. § 1.17(e) and $1,080.00 for the fee for a small entity under 37 C.F.R. § 1.17(a)(5), and a Request for Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is

hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as being attached or enclosed, is being transmitted via First Class U.S. Mail to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Robert A. Hodges — Date 7/13/2006

APPENDIX

Exhibit A	Printout of http://www.activemotif.com/catalog/cell_biology/chariot Printout of http://www.activemotif.com/download/profile/chariot_profile.pdf (Describes the product Chariot™, manufactured by Active Motif, Inc.).
Exhibit B	U.S. Patent 6,841,535 (Description of the Chariot™ signal peptide, attached with the relevant portion highlighted).
Exhibit C	Aoshiba et al., *Journal of Respiratory Cell and Molecular Biology*, 28:555-562 (2003).
Exhibit D	Blair et al., *Journal of Pharmacology and Experimental Therapeutics* 310(3):871-880 (2004).
Exhibit E	Cen et al., *Journal of Biological Chemistry*, 278(10):8837-8845 (2003).
Exhibit F	Chan et al., *Journal of Neurophysiol.*, 94:1037-1047 (2005).
Exhibit G	Chipuk et al., *Science*, 303:1010-1014 (2004).
Exhibit H	Gallo et al., *Journal of Cell Biology*, 158(7):1219-1228 (2002)
Exhibit I	Garnon et al., *Journal of Biological Chemistry*, 280(7):5750-5763 (2005)
Exhibit J	Gehler et al., *Journal of Neuroscience*, 24(47):10741-10749 (2004).
Exhibit K	Bardag-Groce et al., *Experimental and Molecular Pathology*, 74:160-167 (2003).
Exhibit L	Gorska et al., *Journal of Experimental Medicine*, 199(3):369-379 (2004).
Exhibit M	Heerssen et al., *Nature Neuroscience*, 7(6):596-604 (2004).
Exhibit N	Jurney et al., *Journal of Neuroscience*, 22(14):6019-6028 (2002).
Exhibit O	Kashkar et al., *Journal of Experimental Medicine*, 198(2):341-347 (2003).
Exhibit P	Koulen et al., *Investigative Opthalmology & Visual Science*, 46(1):287-291 (2005)
Exhibit Q	Lee et al., *Journal of Biological Chemistry*, 277(51):49341-49351 (2002).

Exhibit R	Li et al, *Journal of Biological Chemistry*, 280(25):23945-23959 (2005).
Exhibit S	Lin et al., *Journal of Biological Chemistry*, 270(24):14255-14258 (1996).
Exhibit T	Lin et al., *Journal of Cell Science*, 117(23):5609-5621 (2004).
Exhibit U	Liu et al., *Proceedings of the National Academy of Sciences*, 93:11819-11824 (1996)
Exhibit V	Maron et al., *Journal of Physiology*, 289(2):L349-L354 (2005).
Exhibit W	Mizukami et al., *Journal of Biological Chemistry*, 279(48):50120-50131 (2004).
Exhibit X	Morris et al., *Nature Biotechnology*, 19(12):1173-1176 (2001).
Exhibit Y	Pandey et al., *Journal of Biological Chemistry*, 278(5):2837-2844 (2003).
Exhibit Z	Peluso et al., *Endocrinology*, 142(10):4203-4211 (2001).
Exhibit AA	Sebbagh et al., *Journal of Experimental Medicine*, 201(3):465-471 (2005).
Exhibit BB	Sorenson, *Journal of Biological Chemistry*, 279(12):11368-11374 (2004).
Exhibit CC	Taneja, et al., *Journal of Biological Chemistry*, 279(3):2273-2280 (2004).
Exhibit DD	Tang, et al., *Proceedings of the National Academy of Sciences*, 100(7):4096-4101 (2003).
Exhibit EE	Taniyama et al., *American Journal of Physiology*, 287:C494-C499 (2004).
Exhibit FF	Tassa, et al., *Biochemical Journal*, 376:577-586 (2003).
Exhibit GG	Van der Wijk, et al., *Journal of Biological Chemistry*, 278(41):40020-40025 (2003).
Exhibit HH	Wu, et al., *The Plant Journal*, 33:131-137 (2003).
Exhibit II	Zhang et al., *Proceedings of the National Academy of Sciences*, 102(8):2802-2807 (2005).
Exhibit JJ	Zhou et al., *Journal of Biological Chemistry*, 276(30):27793-27798 (2001).
Exhibit KK	List of over 500 signal peptides that have been experimentally verified to act as signal peptides in mammals.
Exhibit LL	Jo et al, Nature Biotechnology, 19:929-933 (2001).